NHS England commissioning position on sapropterin for the treatment of phenylketonuria (pku) and tetrahydrobiopterin (bh4) disorders

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Background

On 22 September 2021, the National Institute for Health and Care Excellence (NICE) published Technology appraisal guidance 729: '[Sapropterin for treating hyperphenylalaninaemia in phenylketonuria]'.

The guidance states that 'Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin (response as defined in the summary of product characteristics) in people with phenylketonuria (PKU), only if they are:

- under 18 and a dose of 10 mg/kg is used, only using a higher dose if target blood phenylalanine levels cannot be achieved at 10 mg/kg
- aged 18 to 21 inclusive, continuing the dose they were having before turning 18 or at a maximum dose of 10 mg/kg
- pregnant (from a positive pregnancy test until birth)'.

When NICE considered the use of sapropterin for the treatment of PKU, Kuvan was the only licensed product and the committee was only able to consider and make a recommendation on this product. The committee concluded that it 'was aware that generic products could be available in the near future and hoped these would be priced to allow access to this drug for all adults with PKU.' Based on the committee's preferred assumptions, NICE supported NHS England to explore whether it could commission sapropterin for all adults when generics became available.

As a generic product is now available, NHS England is also commissioning access to sapropterin for **all adults** with PKU, alongside the population specified in the NICE guidance. The drug is also commissioned for individuals with tetrahydrobiopterin (BH4) disorders.

As the generic version of sapropterin is non-inferior to the branded product, clinical teams will prescribe the product with the lowest acquisition cost. This includes patients already on treatment.

About the condition

PKU is a rare genetic disorder. In this disorder, the amino acid phenylalanine (Phe) (found in natural food proteins) cannot be broken down and accumulates in the body. High levels of Phe are extremely toxic to the brain and untreated PKU causes profound brain damage resulting in very low IQ, seizures, muscle stiffness, autism, and persistent behavioural

problems. In pregnancies of women with PKU, the foetus can be affected by high levels of Phe.

Since PKU damage is caused by high levels of Phe, non-drug treatment is a very strict low Phe diet (10% to 20% of a normal diet). An artificial protein mix, with added vitamins and minerals, is taken throughout the day but patients often find this unpleasant.

Treatment with sapropterin

Treatment with sapropterin aims to lower the blood Phe levels to close to or below the European Guideline levels (therapeutic ranges are: 120-360 µmol/l up to 12 years, 13 years onwards 120-600 µmol/l, women who are planning a pregnancy 120-360 µmol/l). Sapropterin treatment sustains Phe control over time, which is generally difficult to achieve with diet alone.

As natural protein intake increases and reliance on supplements is reduced, the diet becomes more manageable, thus improving dietary adherence and improving cognitive outcomes.

Pathway for patients with PKU

Following clinical advice from the Metabolic Services Clinical Reference Group, NHS England has determined that the most timely and equitable way of determining eligibility for treatment with sapropterin is for ALL individuals with PKU (except those who are pregnant and those who have previously proven responsiveness) to have a genetic test to determine if they are likely to be amenable to treatment.

Those patients who are likely to be amenable to treatment will have their Phe levels checked by using sapropterin under the supervision of a specialist metabolic dietician. The testing and responsiveness assessment of patients will be based on the sapropterin responsiveness pathway developed by the British Inherited Metabolic Disease Group[1]. The expected doses for patients will be 10 mg/kg with the flexibility to increase to 20 mg/kg if the Phe levels cannot be managed at lower levels. Treatment is accompanied by a low Phe diet.

Patients can continue treatment after a month of assessment is completed if they have a Phe reduction of at least 30%. Patients must comply with regular monitoring as they will be ingesting increased levels of protein during this time.

After six months of treatment with sapropterin, patients can continue treatment if at least one of the following benefits can be shown:

- Phe control assessed as > 75% Phe levels in target range for age

AND/OR

[1] BIMDG: British Inherited Metabolic Disease Group

- Improved Phe tolerance assessed as ≥100% increase in natural protein intake whilst maintaining > 75 % Phe levels in target range for age

These benefits need to be maintained to continue sapropterin treatment and assessment will continue on a six-monthly basis[2].

Pathway for patients with BH4 deficiencies

Patients with BH4 deficiencies will receive a dose of 2-5 mg/kg/day of sapropterin titrated against Phe levels.

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[2] Each six-month review can be undertaken virtually, as a telephone or video consultation with blood spot results.